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Ovarian cancer diagnosed accidentally during treatment for ruptured ectopic pregnancy: is fertility-sparing surgery a viable alternative? Case report and review of the literature

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Summary

According to cancer incidence statistics, it is estimated that 226,000 women are diagnosed annually with epithelial ovarian cancer (EOC) and 140,000 die of the disease worldwide. Ovarian cancer represents the fourth leading cause of all cancer-related deaths in women, and the first cause of death among all gynecological malignancies. With the constant shift towards later parenthood, the growing incidence of EOC in women of reproductive age is noted. Most young EOC women are concerned with preserving their fertility despite oncological outcomes. Nowadays gynecologic oncologists are being asked to include into their decision-making processes the patients' desire for fertility preserving alternatives. The question remains whether it is possible to use fertility-sparing surgery (FSS) without compromising the survival. In the present report, the authors present a case of a 27-year-old patient with ovarian cancer accidentally diagnosed during surgical treatment of an ectopic pregnancy. In this paper, the proper selection of the patients for the conservative management, oncological safety, indications for subsequent chemotherapy, the risk of relapses, obstetrical outcomes, and further oncological control were analyzed based on the largest and most relevant series outcomes data and recommendations. Numerous recent studies have confirm that FSS in young women with early stage of epithelial ovarian cancer, who wish to preserve their childbearing potential, after appropriate selection, appears a viable and safe option. However, there is still a possibility of relapse and regular oncological control is strongly recommended.

Key words: Epithelial ovarian cancer; Fertility-sparing surgery (FSS); Obstetrical outcome; Ectopic pregnancy.

Introduction

Epithelial ovarian cancer (EOC) represents 80-90% of malignant ovarian neoplasms and is considered to be the first cause of death among all gynecological malignancies. Although the vast majority of EOC cases are diagnosed in postmenopausal women, 3-17% of EOCs occur in patients under the age of 40 and only 3-4% in their younger peers, under the age of 30 [1-4]. Data from European centers show that in 62% of patients < 40 years, the diagnosis is made in the early stages of epithelial ovarian cancer (FIGO Stage I-IIA) [5]. Serous carcinoma is the most common histological type of EOC in young women, with good prognosis in early-stage EOC. The five-year overall survival rate and the recurrence rate in early stages of EOC is 91.1% and 11.5%, respectively [6- 9]. The recurrence rate is higher for patients with FIGO Stage IB (14.7%) and IC (20%) [10]. Clinical outcomes in EOC are significantly associated with tumor differentiation grade. The five-year survival in reproductive-age patients with early EOC (IA, IB) is 96% for highly differentiated (G1) and 70% for moderately differentiated (G2) tumors [10,11]. Among young patients, the diagnosis is made more frequently in early stages of EOC and in most cases the tumor is highly differentiated. Young age has already been reported as a favorable prognostic factor in patients with EOC [12-17].

In the present report, the authors present a case of a 27-year-old patient with ovarian cancer accidentally diagnosed during surgical treatment of an ectopic pregnancy.

Case Report

A 27-year-old female (MC), diagnosed with ovarian cancer, was admitted to the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, in February 2014 to continue oncological treatment. The patient underwent a cesarean section in 2011 and was diagnosed with a nodule in the thyroid right lobe in 2008. No other relevant medical history including hereditary diseases was known.

In December 2013, the patient underwent an urgent surgery following an ectopic pregnancy. Laparoscopy was converted to laparotomy due to massive peritoneal adhesions and bleeding. An adhesion of the omentum major with anterior abdominal wall and an adhesion of the intestine and the uterus were found intraoperatively. A tumor of the left ovary (ten cm in diameter) with bleeding was revealed. The uterus, the right ovary, the right fallopian tube, and other abdominal organs showed no significant changes. The adhesions were lysed and the tumor, together with a part of the left ovary, was

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removed. The course of the surgery was uneventful. The patient was discharged in a good overall condition on postoperative day 3.

The pathological report described the tumor (size: 70×90×50 mm) and the ruptured capsule with signs of tumor invasion. After intersection, the structure of the mass was solid and fine-grained. The microscopic report revealed mucinous adenocarcinoma (G1-intestinal type) in the left ovary, predominantly borderline tumor. There were few foci of invasive adenocarcinoma. The left fallopian tube contained graviditas tubaria.

On admission, the patient underwent a medical examination. Normal vaginal secretion and cervix were presented on speculum examination. Normal-size, mobile uterus, normal right ovary, and resistance of a five-cm diameter in the area of the left ovary were revealed on bimanual examination.

Two management strategies were presented and discussed with the patient. The first one included conservative surgery: left-sided unilateral oophorectomy, omentectomy, selective pelvic and para-aortic lymphadenectomy, multiple peritoneal sampling and endometrial biopsy, with comprehensive surgical staging and the second radical surgery based on hysterectomy and surgical staging. The patient opted for the second option. The radical surgery was performed. Intraoperatively, a few adhesions between the omentum and peritonea were found. On palpation, there were no changes on the liver surface and under the diaphragm. The liquid from the Douglas pouch was sent for cytological examination. Normal-sized uterus was present. The adhesion between the left ovary and the sigmoid was lysed. There was no left fallopian tube. No significant changes in the right ovary and the right fallopian tube were found. There were no significant changes of the retroperitoneal space on palpation. The pelvic peritonea was clean. Hysterectomy and unilateral oophorectomy were performed. The remaining part of the left ovary was removed. Omentectomy, selective pelvic and para-aortic lymphadenectomy, and multiple peritoneal sampling were done. The course of the surgery was uneventful. The patient was discharged in a good overall condition on postoperative day 3.

Adenocarcinoma was shown in the final pathology report in the tissue from the area of the left ovary. The remaining part of the left cystic ovary contained carcinoma mucinosum. Metastases of adenocarcinoma were revealed in the peritoneal sample from the left side. The right ovary, with the corpus luteum and small cysts, and normal right fallopian tube were found. The endometrium was in the secretory phase. The cervix was normal and bilateral parametrium showed no signs of resistance. The lymph nodes were reactive. Normal omentum. There were no tumor cells in the liquid. Classification included pT2aN0, FIGO Stage IIB. Subsequent chemotherapy was indicated.

Discussion

According to cancer incidence statistics, it is estimated that 226,000 women are diagnosed annually with EOC and 140,000 die of the disease worldwide [18]. Ovarian cancer represents the fourth leading cause of all cancer-related deaths in women, and the first cause of death among all gynecological malignancies. In general, ovarian cancer is responsible for 6% of cancer diseases among female patients. In Poland, approximately 3,300 cases of EOC are diagnosed every year. Ovarian cancer is considered to be the fifth most frequent cancer disease, and the fourth cause of cancer-related deaths, in Polish women.

With the constant shift towards later parenthood, the growing incidence of EOC in women of reproductive age is noted. Most young EOC women are concerned with preserving their fertility despite oncological outcomes. The question remains whether it is possible to use fertility-sparing surgery (FSS) without compromising the survival. Both, the patient and the physician should participate in the decision-making process regarding further treatment. According to the literature, FSS seems to be an oncologically safe option for appropriately selected young patients, diagnosed with early EOC with highly differentiated Stage (IA G1). Fertility-sparing treatment is based on unilateral oophorectomy, omentectomy, selective pelvic and para-aortic lymphadenectomy, multiple peritoneal sampling, and endometrial biopsy with comprehensive surgical staging [10, 19]. FSS in patients with advanced stages (IC) and poorly differentiated tumor with strong desire to preserve fertility is still widely discussed. There is no sufficient evidence to confirm its safety in patients with IC, G2/G3 stages.

Preservation of the reproductive tract in young women, especially nulliparous, is a widely natural need. FSS not only offers a possibility of childbearing but also preserves endocrine function of the ovaries. Nevertheless, there is general concern about oncological safety of the conservative management. A number of studies reported pregnancy outcomes and discussed the possibility of an increased risk of recurrences in patients who had undergone FSS [20]. According to American College of Obstetricians and Gynecologists (ACOG) 2007 and European Society of Medical Oncology (ESMO) 2008 recommendations, FSS can be offered to women under the age of 40, with well-differentiated stage (G1/G2) of IA tumor [21-23]. In case of patients with unfavorable histological type of tumor such as clear cell, anaplastic, small-cell, and poorly-differentiated (G3), various authors recommend their exclusion from any fertility-sparing treatment [21-23]. Conservative surgical management is also contraindicated in cases with signs of extra-ovarian spread such as invasion of the capsule or positive peritoneal cytology [23]. According to the review of Zapardiel *et al.*, conservative treatment without subsequent chemotherapy may be considered in young patients with FIGO Stage IA with histological type G1/G2 of the tumor. According to these authors, FSS with second-line chemotherapy can be offered to young women even in Stage IC or in case of poorly differentiated tumor (G3) [6].

In the present case report, both therapeutic procedures were offered to the 27-year-old patient. After oncological, reproductive, and obstetric counseling, the patient resigned from FSS. Oncological safety was the most important factor for the patient. After standard surgical treatment and staging, she was diagnosed with ovarian cancer Stage IIB. According to recommendations, she was deemed ineligible to undergo FSS. In the population-based study by Huber et al., the authors suggested that only a very small proportion of EOC patients are eligible for FSS. Moreover, they

highlighted the importance of appropriate patient selection. In a group of 1 133 women with ovarian cancer, only 11 (0.97%) met the criteria for FSS. However, clinical management does not always follow the recommendations. The patient's final decision of conservative treatment should be respected despite an unfavorable pathological report and even in the case of suspected invasive disease. In these particular cases, the prognosis is based on histological type, FIGO Stage, and the grade of nuclear differentiation. Tingustald *et al.* analyzed 571 patients with EOC in all age groups. The risk of cancer-related death was 2.8 times lower in patients under 45 years of age as compared to patients above 65 years of age [12]. These authors pointed to young age being an independent favorable prognostic factor [12-17]. Another point to be discussed is the obstetrical outcome after fertility-sparing surgery in patients with EOC [24]. The rate of successful pregnancies is encouraging. In the review from 2014, Fotopoulou *et al.* analyzed fertility results after conservative surgery in 697 patients with EOC. Mean age for fertility sparing surgery in different studies was 29 years. Over 60% of women were diagnosed with Stage IA, G1/G2, and chemotherapy was not obligatory after a conservative surgery. A successful conception rate was higher by 70%, with an acceptable 18% abortion rate. Interestingly, only 5% of patients needed assisted reproductive treatment. FSS was also performed in Stage IC and IA with clear-cell cancer in women with strong childbearing desire. In this group, subsequent chemotherapy was strongly recommended. Patients with clear-cell cancer in stages higher than IA and all patients with low grade of nuclear differentiation were excluded from FSS [14]. No congenital abnormalities were reported in the group treated with chemotherapy [6].

From the general standpoint, ovarian cancer that occurs in young nulliparous women is always related to a therapeutic dilemma. As there are no randomized trials confirming the safety of FSS, the final therapeutic decision must be made by the patient. The treating physician is obligated to discuss all therapeutic possibilities with their complications. According to the literature, preservation of fertility and ovarian function in some cases is related with higher risk of recurrences. The FIGO Stage of the disease is considered to be the main prognostic factor of long-term clinical outcome after conservative treatment. Some retrospective studies report FSS in patients with FIGO Stage IIIC and with a strong desire of childbearing. The general rate of recurrences ranges between 11.8-15% [5]. In a recent study of Kajiyama *et al.*, a group of 94 patients with early EOC (IA- 43, IC- 51) after conservative surgery was investigated [25]. The five-year survival in the presented group reached 84.3%. Disease recurrence occurred in 14.9% of patients, and 11% of women died of cancer disease in the course of five years since FSS. Interestingly, there were no statistically significant differences in the recurrence rate in patients with Stage IA as compared to Stage IC. Based on this study, a higher rate of recurrences was directly related to medium or low nuclear differentiation stage (G2/G3) of the tumor. A worse prognosis for patients with G2-3 tumors was confirmed in a review by du Boius *et al.* In this review, the oncological safety of FSS was evaluated in 913 patients with EOC from 15 different clinical studies. Overall, recurrences were detected in 11.4% of women. All studies showed that the rate of relapse is four times higher in the G2-3 group. Moreover, the rate of recurrences was two times more frequent in women with ovarian cancer in Stage IB and IC as compared to those in Stage IA [26].

There is another controversy regarding completion of surgery after childbirth. The retrospective study by Borgfeldt *et al.* presents 23 patients with early ovarian cancer in Stage IA/IB, G1-2, who underwent conservative surgery without subsequent chemotherapy. Radical surgery was offered to all patients who delivered the desired number of children. Prophylactic removal of the remaining ovary and hysterectomy was performed in six women after fulfilling their desire to have more children. All patients were followed–up over a period from 11 to 185 months (median 92). None of the women in Stage IA, G1-2 showed recurrences of the disease [27]. However, the study conducted by Shiota *et al.* on a group of women with EOC highlights that the general risk of relapse in Stage IA, G1-2 is 8% and rises to 11% in Stage IC G1-2 [28].

According to the ACOG criteria, the estimated incidence of FSS-eligible patients is 6.5 women annually [29]. To improve the quality of care for these patients, the authors of the aforementioned study emphasize the need to centralize oncological care in dedicated centers. In some cases patients are diagnosed with cancer by accident. In very rare situations women with undiagnosed EOC undergo urgent surgery because of ovarian torsion or hemorrhagic ovarian tumor. Proper intraoperative evaluation of an ovarian tumor is often difficult [30]. It is uncommon to perform intraoperative pathological exam in urgent cases. In the present case report, a young patient with bleeding of the ectopic pregnancy underwent an urgent surgery. After the final pathological report, the patient without any previous symptoms was diagnosed with ovarian cancer and referred to the oncological care center. After discussing oncological safety and patient desires, a different surgical treatment was offered.

Conclusions

In conclusion, numerous recent studies have shown that FSS in young women with early stage of EOC appears a viable and safe option. The most important concern is appropriate patient selection, based on staging. Subsequent chemotherapy should be considered in every case. According to the current literature, FSS can be offered to young women with Stage IA G1-2 without oncological compro-

mise. In cases of Stage IC and G3, conservative surgery remains controversial. In each case, the patient should be aware of a possible relapse and remain under permanent oncological control.

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